Claims

1. A method of isolating or selecting related DNA molecules harboring nucleic acid differences in a DNA sample, said method comprising the selection or isolation of heteroduplexes containing at least one internal single stranded region with a single stranded trap, wherein

i) said heteroduplexes are formed between said related DNA molecules,

ii) said internal single stranded regions represent said nucleic acid differences, and

iii) the single stranded trap involves the use of a Recognition Element that is benzoylated-naphthoylated-DEAE-cellulose (BNDC).

2. A method of isolating or selecting related DNA harboring nucleic acid differences in a DNA sample, comprising the following steps:

(a) obtaining a DNA sample containing said related DNA molecules;

(b) denaturing DNA molecules present in said sample;

(c) annealing said denatured DNA molecules to allow the formation of heteroduplexes between said related DNA molecules harboring nucleic acid differences; and,

(d) isolating or selecting heteroduplexes containing at least one internal single stranded region using a single-stranded trap comprising a Recognition Element that is benzoylated-naphthoylated-DEAE-cellulose (BNDC).

3. The method of claim 2, wherein said method comprises the steps of reducing the size of DNA molecules.

4. The method of claim 2, wherein said method comprises the steps of:

i) removing single stranded regions other than internal single stranded regions on heteroduplexes containing at least one internal single stranded region by cleaning and blunting DNA molecules obtained after step (c); and, optionally,

ii) ligating adapters to the ends of said heteroduplexes,

wherein said steps are performed before step (d).

5. The method of claim 2, wherein said method comprises a step of amplifying said isolated or selected heteroduplexes.

6. The method of claim 1, wherein said DNA sample comprises DNA molecules from a single source, a single environment or a single physiological condition.

7. The method of claim 1, wherein said DNA sample comprises a mixture of DNA molecules from at least two different sources, two different environments or two different physiological conditions.

8. The method of claim 1, wherein said DNA sample comprises cDNA.

9. The method of claim 1, wherein said DNA sample comprises DNA molecules derived from a single gene or a limited set of genes.

10. The method of claim 1, wherein said method comprises the following steps:

i) mixing said sample with said Recognition Element under condition to allow (a) the binding of said internal single stranded regions within said heteroduplexes to said Recognition Element and (b) subsequent formation of internal single stranded region containing heteroduplex-recognition element complexes; and

ii) separating said complexes from said sample.

11. The method of claim 2, wherein step (d) of said method comprises the following steps:

(i) using benzoylated-naphthoylated-DEAE-cellulose (BNDC) to prepare a column;

(ii) washing said column;

(iii) bringing said column into contact with said annealed sample to allow (a) the binding of said internal single stranded regions with said heteroduplexes to said column and (b) subsequent formation of internal single stranded retion containing heteroduplex-benzoylated-naphthoylated-DEAE-cellulose (BNDC) complexes; and

(iv) removing the unbound DNAs by washing said column.

12. The method of claim 11, wherein:

a. the column is washed with a binding buffer comprising 1M NaCl; and

b. the annealed sample is dissolved in a binding buffer comprising 1M NaCl.

13. The method of claim 11 further comprising the step (v) eluting the internal single stranded region containing heteroduplex with an elution buffer.

14. The method of claim 1, wherein said nucleic acid difference comprises an insertion, deletion, or replacement of at least 15 nucleotides.

15. The method of claim 2, wherein said DNA sample comprises DNA molecules from a single source, a single environment or a single physiological condition.

16. The method of claim 2, wherein said DNA sample comprises a mixture of DNA molecules from at least two different sources, environments or physiological conditions.

17. The method of claim 2, wherein said DNA sample comprises cDNA.

18. The method of claim 2, wherein said DNA sample comprises DNA molecules derived from a single gene or a limited set of genes.

19. The method of claim 2, wherein said nucleic acid difference comprises an insertion, deletion, or replacement of at least 15 nucleotides.

20. The method of claim 2 wherein step (d) of said method is repeated more than one time on the same sample.

21. The method of claim 2 wherein said method comprises an additional step of recovering said related DNA from internal single stranded region containing heteroduplex-recognition element complexes.

22. The method of claim 2 wherein said method comprises a step of cloning said DNA harboring nucleic acid differences.

23. The method of claim 2 wherein said method comprises a step of sequencing said DNA harboring nucleic acid differences.